Martin, R., Kramer, M. S., Patel, R., Rifas-Shiman, S. L., Thompson, J., Yang , S., ... Oken, E. (2017). Effects of Promoting Long-term, Exclusive Breastfeeding on Adolescent Adiposity, Blood Pressure, and Growth Trajectories: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Pediatrics*, *171*(7), [e170698]. https://doi.org/10.1001/jamapediatrics.2017.0698

Effects of promoting longer-term and exclusive breastfeeding on adolescent adiposity, blood pressure, and longitudinal growth trajectories: evidence from the PROBIT cluster-randomized trial

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Word count: Abstract 347, Key points 99, Main text 2,975

Date 22 Feb 2017

Abstract

Importance Evidence that breastfeeding reduces child obesity risk and lowers blood pressure (BP) is based on potentially confounded observational studies.

Objective To investigate the effects of a breastfeeding promotion intervention on adiposity and BP at age 16 years, and on longitudinal growth trajectories from birth.

Design Cluster-randomized Promotion of Breastfeeding Intervention Trial, allocated in 1996-1997 into intervention (n=16) or control arms (n=15).

Setting Belarusian maternity hospitals and affiliated polyclinics.

Participants 17,046 breastfeeding mother-infant pairs, of whom 13,557 (79.5%) children were followed-up at 16.

Intervention Breastfeeding promotion, modeled on the Baby-Friendly Hospital Initiative.

Main Outcome Measures Body mass index (BMI); fat and fat-free mass indices (FMI and FFMI) and percent body fat from bioimpedance; waist circumference; overweight and obesity; height; BP; and longitudinal growth trajectories. The primary analysis was modified intention-to-treat (without imputation for losses to follow-up), accounting for within-clinic clustering.

Results The intervention substantially increased breastfeeding duration and exclusivity compared with the control arm (exclusively breastfed: 45% vs 6% at 3 months, respectively). Mean differences at 16 years between intervention and control groups were: 0.21 kg/m^2 (95%CI:0.06, 0.36) for BMI; 0.21 kg/m^2 (-0.03, 0.44) for FMI; 0.00 kg/m^2 (-0.21, 0.22) for FFMI; 0.71% (-0.32, 1.74) for percent body fat; -0.73 cm (-2.48, 1.02) for waist circumference; 0.05 cm (-0.85, 0.94) for height; -0.54 mmHg (-2.40, 1.31) for systolic BP; and 0.71 mmHg (-0.68, 2.10) for diastolic BP. The odds ratio for overweight/obesity (BMI≥85th vs <85th percentile) was 1.14 (1.02, 1.28) and for obesity (BMI≥95th vs <95th percentile) was 1.09 (0.92, 1.29). The intervention resulted in a more rapid rate of gain in post-infancy height (1 to 2.8 years), weight (2.8 to 14.5 years), and BMI (2.8 to 8.5 years) compared to the control arm. The intervention had little effect on BMI z-score changes after 8.5 years.

Conclusions A randomized intervention that increased the duration and exclusivity of breastfeeding did not lower adolescent obesity risk or BP. On the contrary, the prevalence of overweight/obesity were higher in the

intervention arm. All mothers initiated breastfeeding, so findings may not apply to comparisons of the effects of breastfeeding versus formula-feeding.

Trial Registration isrctn.org: ISRCTN37687716; and clinicaltrials.gov: NCT01561612

Keywords: Breastfeeding, adiposity, stature, blood pressure, growth, childhood

Key points

Question What is the effect of a randomized intervention that increased breastfeeding duration and exclusivity on growth, adiposity and blood pressure (BP) at age 16 years?

Findings Cluster-adjusted mean differences between intervention versus control groups were: BMI 0.21 kg/m^2 (95% CI: 0.06, 0.36) (with similarly positive effects for other adiposity measures); systolic BP -0.54 mmHg (-2.40, 1.31); and diastolic BP 0.71 mmHg (-0.68, 2.10). The cluster-adjusted odds ratio for overweight/obesity was 1.14 (1.02, 1.28) and for obesity was 1.09 (0.92, 1.29).

Meaning A randomized intervention that increased breastfeeding intensity did not reduce obesity or lower BP levels at 16.

Introduction

The prevalence of childhood obesity has risen substantially in recent decades around the world.(1) In turn, obese children are more likely to become obese adults(2) and suffer obesity-related chronic illnesses.(3) However, few interventions to prevent childhood obesity have proven effective.(1, 4) Promoting greater uptake and duration of exclusive breastfeeding is a suggested public health measure to reduce childhood obesity(5) and its metabolic consequences (e.g. high blood pressure, BP).(6) This approach is based on mechanistic studies, for example those finding that the lower protein content of breastmilk (in comparison to formula milk) may reduce adipocyte development,(7) and a body of observational human data suggesting inverse associations of breastfeeding and its duration with later obesity.(6, 8-12) However, observational studies are prone to confounding by social patterning of both breastfeeding and growth,(13) the epidemiological evidence is inconsistent(6, 13-23) and publication bias is a concern.(24, 25) Furthermore, weight and BP change dynamically during development, but most previous studies measure these outcomes on a single occasion, rather than on multiple occasions at different ages among the same individuals.

The Promotion of Breastfeeding Intervention Trial (PROBIT) was designed to overcome limitations inherent in observational studies of the long-term effects of breastfeeding on child outcomes, including adiposity and blood pressure. We cluster-randomized 17,046 children from 31 clinics, born in 1996-1997 to either a control arm or breastfeeding promotion intervention (based on the World Health Organization and United Nations Children's Fund (WHO/UNICEF) Baby-Friendly Hospital Initiative).(26) Trial inclusion criteria required: a) healthy, term (≥ 37 weeks gestation), and normal weight (≥ 2500g) singleton infants with an Apgar score of ≥ 5 at 5 minutes; and b) mothers who initiated breastfeeding with no condition expected to interfere with their ability to breastfeed.(26) The breastfeeding promotion intervention substantially increased breastfeeding duration and exclusivity when compared with the control arm (exclusively breastfed: 45% vs 6% at 3 months and 6.6% vs 0.7% at 6 months).(26) Our trial, therefore, provides a unique opportunity to test, in an intention-to-treat analysis, the extent to which breastfeeding causally influences adiposity, stature and blood pressure, making an important contribution to the debate about whether breastfeeding is protective against obesity.(5, 27)

We previously reported no evidence of a protective effect of the breastfeeding intervention on adiposity or blood pressure at 6.5 and 11.5 years.(28-30) We now analyze these outcomes at 16 years, when the children were beyond adiposity rebound, most had attained (or nearly attained) adult stature, and adiposity and blood pressure measures should better predict adult levels than at earlier ages. In addition to outcomes at single timepoints reported in previous publications, we take advantage of repeated weight and length/height measures taken from birth to adolescence to examine the effects of the intervention on longitudinal growth trajectories, which have not been examined in previous studies of breastfeeding.

METHODS

Randomization

A detailed description of the trial design has previously been published.(26) Briefly, the units of randomization (clusters) were 31 maternity hospitals and their associated outpatient polyclinics (which manage both well and ill children) in Belarus (**Figure 1**). These units were randomized to either: i) a control arm that continued the breastfeeding practices and policies already in effect at the time of randomization (which was typically characterized by a short duration of exclusive breastfeeding, early introduction of other drinks or foods, and weaning at about 3 months)(31); or ii) an experimental intervention arm based on the Baby-Friendly Hospital Initiative.(26)

Follow-up

We have previously reported on anthropometry and BP outcomes between birth and 12 months (anthropometry only(32)), at 6.5 years(28) and at 11.5 years.(29, 30) The outcomes reported in the current follow-up are at mean age 16, measured between September 2012 and July 2015. At the 16-year follow-up, all anthropometric outcomes were measured in duplicate at dedicated research clinics using uniform research-specific equipment. These outcomes were: weight, percent body fat, fat mass and fat-free (lean) mass, measured by foot-to-foot bioelectrical impedance (Tanita TBF 300GS body fat analyzer); waist circumference

measured using a nonstretchable measuring tape; standing height using a wall-mounted stadiometer (Medtechnika) and systolic and diastolic blood pressure measured in duplicate using a digital oscillometric device (705IT; Omron Healthcare, Milton Keynes, United Kingdom). The outcome measurements and their timing for the earlier research visits are summarized in **eTable 1**.

Training and quality assurance procedures have been described in detail.(26, 28, 29, 33) Our quality assurance processes raised concerns about the validity of the 16-year follow-up data from one polyclinic (N=267 originally enrolled), and we therefore excluded the 16-year data from this clinic in the current analysis. In the remaining 30 polyclinics (15 intervention, 15 control), the children were followed up by one or two research pediatricians depending on clinic volume.

Derived variables

Duplicate measures of height and waist circumference were taken; if the measurements differed by more than 0.5 cm, third (and fourth, if necessary) measurements were taken and all readings averaged. We calculated body mass (BMI), fat mass (FMI), and fat-free mass (FFMI) indices as weight, fat mass, and fat-free mass in kilograms divided by height in meters squared. We calculated waist-to-height ratio by dividing waist circumference in centimeters by standing height in centimeters. We defined overweight as BMI between the 85^{th} to $<95^{th}$ percentiles and obesity as BMI at or above the 95^{th} percentile, based on the Centers for Disease Control and Prevention (CDC) 2000 age- and sex-specific reference data.(34) We used three dichotomous outcomes: BMI $\geq 95^{th}$ percentile vs $<95^{th}$ percentile, BMI $\geq 85^{th}$ percentile vs $<85^{th}$ percentile, and BMI ≥ 25 kg/m^2 vs <25 kg/m^2. For the longitudinal trajectory analysis, BMI z-scores were calculated using the WHO standard/reference.(35-37)

The analyses of growth trajectories included 17,042 (99%) children with at least one measurement of weight, length (to age 2 years) or height (after 2 years). We parameterized the relationships of weight, stature or BMI z-score with age using linear splines with 5 knot points at 3 months, 12 months, 2.8 years, 8.5 years and 14.5 years to describe periods of approximately linear growth based on the data.(38) Although a linear spline

model is an approximation of the true non-linear growth function, its coefficients are easily interpretable and have produced a good model fit in this and other cohorts.(39-44) The knot points at 8.5 and 14.5 years were chosen because those were the oldest ages at the 6.5- and 11.5-year follow-ups. Setting the knot points at the median (or 25% or 75%) age of the 6.5- and 11.5-year follow-ups, resulted in similar findings.

The parent or guardian (usually the mother) who accompanied the child at the 6.5-year follow-up reported weight and height for herself and her partner; at the 11.5-year follow-up we measured mother's weight and height if she attended. The most recent measurements of parental height and calculated BMI were used for analysis.

Reproducibility

Audit visits were conducted to assess inter-observer reproducibility of the outcome measurements, an important feature, given that blinding of pediatricians to the intervention vs control group assignment was not feasible. In the 24 lower-volume polyclinics with a single pediatrician, 4 children were randomly selected to return for re-measurement of all variables. For the 6 higher-volume clinics with 2 study pediatricians, 3 children per pediatrician were selected. Thus, a total of 132 children were audited. So that all children seen in follow-up were eligible for the repeated measurements, the selection was carried out after completion of primary data collection, an average of 1.2 years (range, 0.02-2.5) after the initial visit. The audit was carried out by 1 of 3 Minsk-based pediatricians not involved in primary data collection and blinded to the measures obtained at the initial visit but not to trial arm. Because of the time elapsed between the audit and initial visits, reproducibility was assessed using Pearson correlation coefficients.

Governance and ethics

The 16-year follow-up was approved by the Belarussian Ministry of Health and received ethical approval from the McGill University Health Centre Research Ethics Board, the Institutional Review Board at Harvard Pilgrim Health Care and the Avon Longitudinal Study of Parents and Children (ALSPAC) Law and Ethics Committee. A parent or legal guardian provided informed consent in Russian at enrollment and at all follow-

up visits, and all children provided written assent at the 11.5- and 16-year clinic visits.

Statistical analysis

Comparisons between the intervention and control groups were based on a modified intention-to-treat analysis without imputation for missing outcome data (i.e., based on the 13,557 children with observed outcomes). We accounted for possible non-independence of measurements within individual clinics (clustering) using mixed-effects models. In a sensitivity analysis, we used SAS multiple imputation for N=17,046 individuals to impute 20 values for each missing observation (including outcomes at 16 years) and combined multivariable modeling estimates using Proc MI ANALYZE in SAS (see Supplementary materials(45, 46)). For the trajectory analyses we employed a three-level multilevel model: i) measurement occasion; ii) individual child; and iii) clinic site where the child was examined; these analyses were conducted in STATA version 13.1 (StataCorp. 2013. College Station, TX: StataCorp LP)(47) and MLwiN version 2.36.(48)

Results are presented for: i) the simple cluster-adjusted model; ii) the model after additional adjustment for age at follow-up and baseline characteristics: stratum-level variables (urban vs rural and East vs West Belarus residence), maternal and paternal education, child sex, and birth weight (for adiposity, standing height and blood pressure outcomes); iii) the model after further adjustment for measured parental BMI (for adiposity and weight gain), parental height (for child height outcomes) or parental BMI and height (for blood pressure and BMI gain). Models ii) and iii) were implemented in case of baseline imbalances, given the relatively small number of randomized clusters.

The intention-to-treat analysis likely underestimates the magnitude of effect of breastfeeding exclusivity and duration, owing to overlap in breastfeeding between the randomized groups – many intervention mothers did not exclusively breastfeed for 3 or 6 months, and some control mothers did. In a secondary analysis, we applied instrumental variable methods(49) to account for non-adherence. The instrumental variable analysis robustly estimates the causal effect of having been exclusively breastfed for ≥3 months (versus <3 months), using randomization status as an instrument (i.e., a variable causally related to exclusive breastfeeding but not

to the adiposity outcomes, except through breastfeeding), assuming that randomization status is independent of any confounders of the exposure-outcome relationships. As such, the effect estimates from instrumental variable analyses are not affected by measured or unknown variables that may confound the exposure-outcome association. We performed instrumental variable estimation of continuous outcomes using the generalized 2-stage least squares estimator, and of dichotomous outcomes using a probit model for instrumental variable analysis,(50) both of which account for within-clinic clustering.

For comparison with previous observational studies, we conducted observational analyses (i.e., disregarding randomization status) to estimate associations of the duration of any or exclusive breastfeeding on the same outcomes as the intention-to-treat analysis, also accounting for clustering and the same baseline characteristics as described above, using multiple linear regression for continuous outcomes and multiple logistic regression for dichotomous outcomes. In a sensitivity analysis, we stratified the results by whether or not the children correctly identified their originally allocated trial arm to determine if this knowledge biased the outcomes.

To provide context, we also present the observational associations of study outcomes with other non-breastfeeding baseline characteristics previously suggested to be early-life determinants of overweight and obesity.

RESULTS

A total of 13,557 children were examined at a median age of 16.2 years (SD, 0.5; IQR, 15.8-16.4), representing 79.5% of the 17,046 originally randomized and 80.8% of the 16,779 from included sites (**Figure 1**). Follow-up rates were similar in the intervention (82%) and control (79%) arms overall, although they varied from 41% to 98% at the different clinics. The children followed-up at 16 years in the intervention and control groups were similar in baseline characteristics, with small differences paralleling those previously reported at randomization (**Table 1**).(26) The audit showed high correlations (Pearson r $\geq$0.83) between initial clinic results and blinded repeat measures of weight, fat mass, fat-free mass, percent fat, waist circumference and standing height. The correlations were lower for systolic (r=0.55) and diastolic (r=0.37)

blood pressure (**eTable 2**). All 16-year outcome measures showed a low degree of within-polyclinic clustering (ICC range 0.003–0.09).(33)

The results of the primary analysis are shown in **Table 2**. There was little consistent evidence that the intervention-effects differed in boys compared to girls (P values for sex-interactions in **Table 2**). The raw mean values of BMI, fat mass index, percent body fat, standing height and blood pressure, and the prevalence of overweight and obesity, were slightly higher in the intervention vs control arms. The cluster-adjusted odds ratio for overweight/obesity was 1.14 (95% CI, 1.02 to 1.28) and for obesity was 1.09 (95% CI, 0.92 to 1.29). Further controlling for baseline (**Table 2**) and parental characteristics (**eTable 3**), or multiply imputing outcomes (**eTable 4 and eMethods**), did not alter these conclusions.

Compared to the control arm, infants in the intervention arm had more rapid weight and length gain in the first 3 months, followed by lower weight and length gain between 3-12 months (**Table 3 and Figure 2**), as reported previously(32). In the present updated analysis, we found that the intervention resulted in more rapid growth in length than the control arm between 1 and 2.8 years, and in more rapid weight gain between 2.8 and 14.5 years. The rate of BMI change between 2.8 and 8.5 years was slightly higher in the intervention arm, reflecting the greater weight gain during this period. Sex-specific results are presented in **eTable 5**.

Using multilevel models to estimate mean differences in weight, height and BMI z-scores between intervention and control groups at the mean clinic age revealed differences broadly in line with the cluster-adjusted estimates (**Figure 2**). Although children were heavier in the intervention compared to the control arm, they were also taller, and their BMI z-scores showed little overall difference from mid-childhood.

The instrumental variable results are in line with those of the primary analysis (**Table 4**). Overall, 32.1% of the intervention group and 25.4% of the control group correctly identified the randomization arm to which they belonged, but such knowledge made little difference to the effect estimates (data not shown). In observational analyses, increased duration of exclusive (**eTable 6)** or any (**eTable 7**) breastfeeding was

positively associated with several measures of adiposity, in line with the intention-to-treat results. **eTable 8** presents the association of baseline characteristics with BMI category at 16 years. Estimates were in the expected direction for several sociodemographic and early-life variables.

COMMENT

In this large cluster randomized controlled trial, an intervention to promote increased duration and exclusivity of breastfeeding did not reduce levels of general or central adiposity or lower BP in children aged 16 years. Beyond infancy, the intervention resulted in more rapid growth in height and then more rapid weight gain in early and mid-childhood, respectively, but the intervention had little effect on BMI z-scores after 8.5 years.

Our findings are similar to results in the same children at age 6.5 years and 11.5 years.(28, 29) The minimal imbalances in baseline characteristics at enrollment and amongst those followed up provide reassurance that the randomization was successful and that confounding and selection bias are unlikely explanations for the results. In an observational analysis, we did not observe the inverse associations of increased breastfeeding with overweight and obesity reported in previous observational studies, possibly due to differences in confounding structures in Belarus compared to Western countries. The Pelotas (Brazil) cohort found no association of socioeconomic position with breastfeeding, and no strong association of breastfeeding with BMI or BP (similar to our observational analysis in Belarus).(13) This contrasts with the ALSPAC cohort, UK, in which higher socioeconomic position was strongly associated with increased breastfeeding, and breastfeeding was associated with lower BMI and BP, even after adjusting for socioeconomic position.(13) Such cross-cohort comparisons suggest that reported associations of breastfeeding with child BMI and BP in ALSPAC are likely to reflect residual confounding.(13)

Higher-than-expected breastfeeding duration was observed in the control group, which may have been due to deteriorating economic conditions in Belarus during the trial and the higher cost of formula.(26) Nonetheless, the intervention led to a substantial increase in breastfeeding duration and exclusivity compared to the control

arm.(26) Breastfeeding was initiated in all study participants, so our findings may not apply to comparisons of breastfeeding versus formula feeding. Given the (expected) overlap in breastfeeding in the intervention and control arms, we used instrumental variable analysis to estimate unconfounded associations of the difference in breastfeeding exclusivity and duration achieved between the two randomized groups with adiposity and BP. The instrumental variable analysis supports our primary findings that the breastfeeding promotion intervention did not substantially lower the outcomes of interest. The small positive associations of the intervention with overweight and obesity could be a chance finding, but we cannot exclude a true increase in risk caused by the intervention. One suggested physiological mechanism whereby prolonged breastfeeding could increase the risk of obesity is longer exposure to maternal hormones present in breastmilk, which could theoretically alter the infant's lipid metabolism and increase body fat composition in later life.(51)

Belarus has low overall levels of obesity and overweight (in our study, 4-5% were obese and 13-15% were overweight or obese at 16 years). Hence, our findings may not be generalizable to other settings with higher prevalence of overweight and obesity. Whilst many observational studies suggest that longer-term and exclusive breastfeeding reduces childhood obesity risk,(6) these studies are prone to confounding by life-style factors and publication bias.(27)

Conclusions

An intervention that achieved substantially greater duration and exclusivity of breastfeeding in Belarus did not prevent overweight or obesity, or lower BP levels at age 16 years, despite differences in growth rates between the trial arms at various ages. On the contrary, overweight and obesity were more prevalent in the breastfeeding promotion intervention arm. While there are many reasons for promoting breastfeeding duration and exclusivity, our trial does not indicate that breastfeeding prevents obesity or lowers BP in childhood or adolescence.

Acknowledgements

Author Contributions: Professor Martin and Ms. Rifas-Shiman had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Obtained funding: Martin, Kramer, Oken.

Administrative, technical, or material support: Martin, Patel, Vilchuck, Bogdanovich, Hameza, Thompson, Oken.

Study supervision: Martin, Kramer, Vilchuck, Bogdanovich, Oken.

Conflict of Interest Disclosures: None

Funding/Support: This study was supported by grants from: Canadian Institutes of Health Research (MOP-53155); and USA National Institutes of Health (R01 HD050758). Prof Oken was supported by US National Institute of Health (K24 HD069408, P30 DK092924). Profs Martin and Tilling work in the Integrative Epidemiology Unit (IEU) supported by the United Kingdom Medical Research Council (MRC) and the University of Bristol (Grant Code: MC_UU_12013/1-9). The NIHR Bristol Nutrition Biomedical Research Unit is funded by the National Institute for Health Research (NIHR) and is a partnership between the University Hospitals Bristol NHS Foundation Trust and the University of Bristol.

Role of the Sponsors: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Acknowledgments: We are grateful to the cohort members, their parents and the study pediatricians and auditors who participated so willingly in the study.

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Figure Legend

Figure 1. Flow diagram of progress of clusters and individuals through PROBIT recruitment and follow-up phases I, II, III and IV.

[a] During PROBIT III, 6 deaths were reported in the intervention arm. Data checking during PROBIT IV found one of these children had been incorrectly reported as deceased and data were amended.
[b] Of the 13557 seen at PROBIT IV, 12072 were seen at both PROBIT II & III, 274 were not seen at either PROBIT II & III, 449 were seen at PROBIT II but not seen at III, and 762 were seen at PROBIT III but not seen at II. Of the 3489 children randomized but not followed up at 16 years, 267 attended the excluded site, 116 died since randomization, 2674 were lost to follow- up, and 432 were unable or unwilling to come for their clinic visit.

Figure 2: Predicted difference in mean weight, height and BMI z-score (with 95% confidence intervals) in the intervention arm compared to control arm.

Predicted size in the intervention compared to the control at age 1, 6.5, 11.5 and 16.2 years

Table 1. Baseline characteristics (N = 13557)

Characteristic	Total N = 13557	Intervention N = 7064	Control N = 6493
Measured at child's birth			
Maternal age, years: N (%)			
<20	1820 (13.4)	979 (13.9)	841 (13.0)
20-34	11173 (82.4)	5792 (82.0)	5381 (82.9)
≥35	564 (4.2)	293 (4.1)	271 (4.2)
Maternal education: N (%)			
Completed university	1842 (13.6)	1002 (14.2)	840 (12.9)
Advanced secondary or partial university	6925 (51.1)	3365 (47.6)	3560 (54.8)
Common secondary	4318 (31.9)	2406 (34.1)	1912 (29.4)
Incompleted secondary	472 (3.5)	291 (4.1)	181 (2.8)
Paternal education: N (%)			
Completed university	1737 (12.8)	936 (13.3)	801 (12.3)
Advanced secondary or partial university	6205 (45.8)	2910 (41.2)	3295 (50.7)
Common secondary	4883 (36.0)	2828 (40.0)	2055 (31.6)
Incompleted secondary or unknown	732 (5.4)	390 (5.5)	342 (5.3)
Stratum-level variable: N (%)			
East/Urban	4150 (30.6)	2215 (31.4)	1935 (29.8)
East/Rural	2152 (15.9)	1075 (15.2)	1077 (16.6)
West/Urban	3524 (26.0)	2296 (32.5)	1228 (18.9)
West/Rural	3731 (27.5)	1478 (20.9)	2253 (34.7)
Number of older children in household: N (%)			
0	7707 (56.8)	4152 (58.8)	3555 (54.8)
1	4717 (34.8)	2365 (33.5)	2352 (36.2)
2+	1133 (8.4)	547 (7.7)	586 (9.0)
Maternal smoking during pregnancy: N (%)			
No	13287 (98.0)	6898 (97.7)	6389 (98.4)
Yes	270 (2.0)	166 (2.3)	104 (1.6)
Child sex: N (%)			
Female	6576 (48.5)	3474 (49.2)	3102 (47.8)
Male	6981 (51.5)	3590 (50.8)	3391 (52.2)
Birth weight, kg: Mean (SD)	3.44 (0.42)	3.44 (0.42)	3.44 (0.42)

SD = standard deviation.

Table 2. Modified intention-to-treat analysis (without imputation) showing differences in adiposity measures, height and blood pressure comparing intervention vs control groups

	Intervention		Control		Difference in mean (95% CI)				
Outcome at 16 years (N = 13557)	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**Cluster adjusted**	**p-value**	**P for sex int.**	**Further adjusted for baseline factors and age at follow-up[a]**	**p-value**
BMI, kg/m^2	7057	21.5 (3.4)	6480	21.2 (3.3)	0.21 (0.06, 0.36)	0.01	0.92	0.19 (0.04, 0.34)	0.01
FMI, kg/m^2	6997	4.2 (2.6)	6462	4.0 (2.5)	0.21 (-0.03, 0.44)	0.09	0.41	0.20 (-0.01, 0.42)	0.06
FFMI, kg/m^2	6997	17.2 (2.1)	6462	17.2 (2.1)	0.00 (-0.21, 0.22)	0.98	0.13	0.00 (-0.21, 0.21)	1.00
Body fat, %	7043	18.9 (9.0)	6462	18.2 (8.8)	0.71 (-0.32, 1.74)	0.18	0.02	0.69 (-0.26, 1.64)	0.16
Waist circumference, cm	7061	73.6 (8.5)	6482	74.7 (8.1)	-0.73 (-2.48, 1.02)	0.41	<.001	-0.44 (-2.13, 1.24)	0.60
Waist-to-height ratio (x 100)	7059	43.2 (4.7)	6479	43.9 (4.6)	-0.45 (-1.50, 0.59)	0.92	0.97	-0.30 (-1.25, 0.64)	0.82
Standing height, cm	7061	170.4 (8.5)	6489	170.3 (8.5)	0.05 (-0.85, 0.94)	0.40	<.001	0.08 (-0.60, 0.76)	0.53
Systolic BP, mm Hg	7061	120.5 (11.7)	6484	119.9 (11.1)	-0.54 (-2.40, 1.31)	0.57	0.64	-0.48 (-2.10, 1.13)	0.56
Diastolic BP, mm Hg	7061	68.8 (7.6)	6484	67.8 (7.0)	0.71 (-0.68, 2.10)	0.32	0.14	0.52 (-0.73, 1.76)	0.41
		N (%)		**N (%)**	**Odds Ratio (95% CI)**			**Odds Ratio (95% CI)**	
BMI ≥25 vs <25 kg/m^2		892 (12.6)		696 (10.7)	1.20 (1.06, 1.37)	0.004	0.85	1.19 (1.04, 1.35)	0.01
BMI ≥85th vs <85th %ile[b]		1026 (14.5)		842 (13.0)	1.14 (1.02, 1.28)	0.03	0.76	1.15 (1.01, 1.30)	0.04
BMI ≥95th vs <95th %ile[b]		319 (4.5)		270 (4.2)	1.09 (0.92, 1.29)	0.31	0.53	1.12 (0.94, 1.33)	0.20

BMI = body mass index; BP = blood pressure; CI = confidence interval; FMI = fat mass index; FFMI = fat free mass index; SD = standard deviation; Sex int. = sex interaction.

[a] *Additionally adjusted for stratum-level variables (urban vs rural and East vs West Belarus residence), maternal and paternal education, child sex, birth weight and age at follow-up*

[b] *Based on Centers for Disease Control and Prevention (CDC) 2000 reference data.(34)*

Table 3. Modified intention-to-treat analysis (without imputation) showing differences in growth trajectories comparing intervention vs control groups

	Intervention	Control	Difference in mean (95% CI)				
	Mean (95% CI)	Mean (95% CI)		p-	P for	Further adjusted for	p-
Growth (N = 17042)	**N = 8864**	**N = 8178**	**Cluster adjusted**	**value**	**sex int.**	**baseline factors[a]**	**value**
Birth weight, kg	3.4 (3.38, 3.41)	3.38 (3.37, 3.4)	0.01 (-0.01, 0.04)	0.38	0.02[b]	0.02 (-0.01, 0.04)	0.17
Weight gain, kg/year:							
Birth-3m	11.4 (11.35, 11.45)	11.05 (11, 11.1)	0.35 (0.28, 0.42)	<.001		0.32 (0.25, 0.39)	<.001
>3-12m	6.17 (6.14, 6.19)	6.29 (6.26, 6.31)	-0.12 (-0.16, -0.08)	<.001		-0.09 (-0.12, -0.05)	<.001
>1-2.8y	1.81 (1.79, 1.83)	1.8 (1.78, 1.82)	0.01 (-0.02, 0.04)	0.48		0.01 (-0.03, 0.04)	0.69
>2.8-8.5y	2.26 (2.24, 2.28)	2.18 (2.16, 2.19)	0.08 (0.06, 0.11)	<.001		0.07 (0.04, 0.1)	<.001
>8.5-14.5y	4.65 (4.6, 4.7)	4.58 (4.53, 4.63)	0.07 (0, 0.14)	0.04		0.09 (0.02, 0.16)	0.01
>14.5-18.9y	4.62 (4.45, 4.78)	5.01 (4.83, 5.19)	-0.39 (-0.63, -0.15)	0.002		-0.29 (-0.52, -0.07)	0.01
Birth length, cm	51.69 (51.46, 51.91)	51.86 (51.63, 52.09)	-0.17 (-0.49, 0.16)	0.31	<.001[b]	-0.05 (-0.35, 0.24)	0.73
Stature gain, cm/year:							
Birth-3m	37.9 (37.7, 38.09)	36.12 (35.91, 36.32)	1.78 (1.5, 2.06)	<.001		1.24 (0.97, 1.52)	<.001
>3-12m	20.98 (20.9, 21.07)	21.24 (21.15, 21.32)	-0.25 (-0.37, -0.14)	<.001		-0.3 (-0.42, -0.18)	<.001
>1-2.8y	9.83 (9.76, 9.91)	9.62 (9.54, 9.7)	0.22 (0.11, 0.33)	<.001		0.16 (0.05, 0.27)	0.005
>2.8-8.5y	6.87 (6.84, 6.91)	6.86 (6.82, 6.9)	0.01 (-0.04, 0.07)	0.65		0.04 (-0.01, 0.1)	0.11
>8.5-14.5y	5.2 (5.16, 5.24)	5.23 (5.18, 5.27)	-0.03 (-0.09, 0.04)	0.39		-0.06 (-0.12, 0.01)	0.08
>14.5-18.9y	3.23 (3.07, 3.39)	3.67 (3.5, 3.85)	-0.44 (-0.68, -0.21)	<.001		-0.26 (-0.45, -0.07)	0.007
BMI at birth, z-score	-0.52 (-0.58, -0.46)	-0.62 (-0.68, -0.56)	0.1 (0.01, 0.19)	0.03	0.3[b]	0.06 (-0.02, 0.15)	0.15
BMI gain, z-score/year:							
Birth-3m	1.66 (1.56, 1.76)	1.79 (1.69, 1.9)	-0.13 (-0.27, 0.01)	0.07		0.01 (-0.14, 0.15)	0.92
>3-12m	1.8 (1.76, 1.83)	1.95 (1.92, 1.99)	-0.16 (-0.21, -0.11)	<.001		-0.12 (-0.16, -0.07)	<.001
>1-2.8y	-0.5 (-0.52, -0.49)	-0.49 (-0.51, -0.48)	-0.01 (-0.04, 0.02)	0.47		-0.01 (-0.03, 0.02)	0.67
>2.8-8.5y	-0.07 (-0.08, -0.07)	-0.1 (-0.11, -0.09)	0.03 (0.02, 0.04)	<.001		0.01 (0, 0.03)	0.02
>8.5-14.5y	0.06 (0.05, 0.07)	0.07 (0.06, 0.08)	-0.01 (-0.02, 0)	0.07		0 (-0.01, 0.02)	0.56
>14.5-18.9y	-0.08 (-0.1, -0.06)	-0.11 (-0.13, -0.08)	0.02 (0, 0.05)	0.10		0 (-0.03, 0.03)	0.81

BMI = body mass index; CI = confidence interval; m = months; y = years; Sex int. = sex interaction.

[a] Additionally adjusted for stratum-level variables (urban vs rural and East vs West Belarus), both maternal and paternal education and child sex.[b] P-value for sex interaction for entire trajectory.

Table 4. Instrumental variable and observational associations analysis of duration of exclusive breastfeeding (≥3 months vs <3 months) with adiposity measures, height and blood pressure at 16 years

(N = 13557)	*Instrumental variable results* *Exclusive breastfeeding ≥3 vs <3 months*		*Observational analysis* *Exclusive breastfeeding ≥3 vs <3 months*	
	Cluster adjusted	**Further adjusted for baseline factors and age at follow-up[a]**	**Cluster adjusted**	**Further adjusted for baseline factors and age at follow-up [a]**
Continuous outcomes	**Difference in mean (95% CI)**		**Difference in mean (95% CI)**	
BMI, kg/m^2	0.55 (0.09, 1.00)	0.49 (-0.01, 0.99)	0.19 (0.05, 0.33)	0.19 (0.05, 0.33)
FMI, kg/m^2	0.54 (-0.12, 1.20)	0.52 (-0.28, 1.31)	0.09 (-0.03, 0.20)	0.06 (-0.04, 0.16)
FFMI, kg/m^2	0.01 (-0.59, 0.61)	0.01 (-0.65, 0.66)	0.09 (0.00, 0.18)	0.11 (0.04, 0.18)
Body fat, %	1.87 (-1.05, 4.79)	1.76 (-1.71, 5.23)	0.23 (-0.16, 0.62)	0.12 (-0.18, 0.42)
Waist circumference, cm	-1.93 (-6.74, 2.88)	-1.15 (-5.31, 3.02)	0.23 (-0.13, 0.59)	0.22 (-0.13, 0.57)
Waist-to-height ratio (x 100)	0.12 (-2.08, 2.33)	0.19 (-1.39, 1.78)	0.10 (-0.28, 0.47)	0.05 (-0.23, 0.33)
Standing height, cm	-1.20 (-4.16, 1.76)	-0.78 (-3.12, 1.55)	0.10 (-0.10, 0.30)	0.11 (-0.09, 0.31)
Systolic BP, mm Hg	-1.46 (-6.67, 3.76)	-1.21 (-4.93, 2.52)	-0.08 (-0.57, 0.42)	-0.04 (-0.50, 0.42)
Diastolic BP, mm Hg	1.88 (-2.04, 5.80)	1.32 (-2.71, 5.35)	0.22 (-0.10, 0.53)	0.20 (-0.11, 0.52)
Dichotomous outcomes	**Odds Ratio (95% CI)**		**Odds Ratio (95% CI)**	
BMI ≥25 vs <25 kg/m^2	1.51 (1.11, 1.17)	1.43 (1.08, 1.16)	1.20 (1.06, 1.36)	1.20 (1.06, 1.36)
BMI ≥85th vs <85th %ile[b]	1.36 (1.03, 1.15)	1.35 (1.02, 1.16)	1.17 (1.04, 1.31)	1.17 (1.04, 1.31)
BMI ≥95th vs <95th %ile[b]	1.18 (0.87, 1.17)	1.24 (0.89, 1.18)	1.00 (0.83, 1.21)	1.02 (0.84, 1.23)

BMI = body mass index; FMI = fat mass index; FFMI = fat free mass index.

[a] *Adjusted for stratum-level variables (urban vs rural and East vs West Belarus residence), maternal and paternal education, child sex, birth weight and age at follow-up*

[b] *Based on Centers for Disease Control and Prevention (CDC) 2000 reference data.(34)*